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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,633	11/25/1997	ELAZAR RABBANI	ENZ-53	4639

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
08/17/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/978,633	RABBANI ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *245-251,253,261-265,306 and 307* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *245-251,253,261-265,306 and 307* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-22-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 5-22-10.

Claims 245-251, 253, 261-265, 306 and 307 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5-22-10 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed.

Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 245-248, 251, 253, 261-265, 306 and 307 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 275, 289, 290, 296-301 of copending Application No. 08/978,634 for the reasons of record set forth in the Office action mailed 11-23-09. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to methods and cell delivery compositions comprising covalently bound polynucleotides, targeting ligands and polypeptides.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No arguments have been made concerning this rejection.

Claims 245-248, 251, 253, 261-265, 306 and 307 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-5 of copending Application No. 11/929,897

for the reasons of record set forth in the Office action mailed 11-23-09. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to cell delivery compositions comprising covalently bound polynucleotides, targeting ligands and optionally further comprising polypeptides.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No arguments have been made concerning this rejection.

Rejections Necessitated by Amendments

Applicant's arguments with respect to claims 245-248, 251, 253, 261-265, 306 and 307 have been considered but are moot in view of the new ground(s) of rejection set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 245-251, 253, 261-265, 306 and 307 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to kits and methods of administering nucleic acid compositions to any cell in an organism comprising introducing nucleic acid constructs comprising a first, second and third nucleic acid strand, which first nucleic acid strand is circular, is hybridized to the second nucleic acid strand to from a double stranded portion, and which first nucleic acid strand is also hybridized to a third nucleic acid strand in forming a gapped circle, and which second nucleic acid strand is fully complementary and hybridizes with the first nucleic acid strand, and which second nucleic acid strand is double stranded and forms a template for synthesis of a nucleic acid product when present in a prokaryotic or eukaryotic cell, and which third nucleic acid strand also comprises a tail which is covalently attached to an antibody, and also hybridizes to a fourth nucleic acid strand, which is also covalently attached to an antibody. The claims are also drawn to compositions comprising any non-natural entity comprising a first domain which binds non-covalently to a specific nucleic acid component and comprises a linear nucleic acid strand that is complementary to a specific nucleic acid component, and further comprising a second domain which is an entity that binds non-covalently to a cell of interest, and which second domain is separated from the first domain by extension of a specific nucleic acid strand which comprises two separate double stranded regions, one which is bound to the non-natural entity and hybridizes with the first domain's nucleic acid strand, and wherein the second double stranded region forms either through self

complementary sequence or hybridizes to a third nucleic acid strand, and which specific nucleic acid component directs synthesis of a nucleic acid product.

The specification and claims do not adequately describe the distinguishing features or attributes concisely shared by the members of the expansive genus of nucleic acid constructs. This genus reads on a broad array of structures (e.g. thousands and thousands of structures), and the disclosure fails to provide a representative number of species for such a broad genus providing cell delivery to any cell in an organism in vivo or in vitro. The specification and claims do not adequately describe a representative number of species for the very broad genus claimed, nor do they adequately describe the elements essential for this genus.

The disclosure teaches schematics of nucleic acid constructs comprising multiple nucleic acid components (3 and 4 segment components) and domains for target cell binding (see figures 4, 6, 15-8) and for recombinant expression in a target cell. But no reductions to practice have been provided for the instant schematics, whereby the proposed structures are successfully targeted to, and transfected into target cells, remain intact as schematically depicted, and produce the recombinant nucleic acids or protein expression products in a predictable manner.

Concise structural features that would distinguish structures within the broadly claimed genus of sequences are missing from the disclosure (e.g. How many nucleotide residues are required for inter-strand hybridization to keep the proposed constructs intact in a cell, or prior to being taken up by a target cell in an organism? What recombinant products have been successfully expressed in

any prokarytic or eukaryotic target cells from the proposed constructs?). One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to concretely describe the broad genus claimed, and which provide for the functions claimed, of being successfully transformed into a desired target cell in an organism, and of successfully expressing recombinant constructs in a target cell in vitro or in vivo).

Thus, Applicant was not in possession of the expansive genus of constructs claimed.

Claims 245-251, 253, 261-265, 306 and 307 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the depiction of self-annealing, multi-component systems in schematics as illustrated in Figures 4, 6, 15-18, does not reasonably provide enablement for making and using a representative number of species of the genus of constructs claimed, wherein the constructs are assembled, transfected into target cells in vitro or in vivo, and produce and express the recombinant products encoded therein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to kits and methods of administering nucleic acid compositions to any cell in an organism comprising introducing nucleic acid constructs comprising a first, second and third nucleic acid strand, which first nucleic acid strand is circular, is hybridized to the second nucleic acid strand to

from a double stranded portion, and which first nucleic acid strand is also hybridized to a third nucleic acid strand in forming a gapped circle, and which second nucleic acid strand is fully complementary and hybridizes with the first nucleic acid strand, and which second nucleic acid strand is double stranded and forms a template for synthesis of a nucleic acid product when present in a prokaryotic or eukaryotic cell, and which third nucleic acid strand also comprises a tail which is covalently attached to an antibody, and also hybridizes to a fourth nucleic acid strand, which is also covalently attached to an antibody. The claims are also drawn to compositions comprising any non-natural entity comprising a first domain which binds non-covalently to a specific nucleic acid component and comprises a linear nucleic acid strand that is complementary to a specific nucleic acid component, and further comprising a second domain which is an entity that binds non-covalently to a cell of interest, and which second domain is separated from the first domain by extension of a specific nucleic acid strand which comprises two separate double stranded regions, one which is bound to the non-natural entity and hybridizes with the first domain's nucleic acid strand, and wherein the second double stranded region forms either through self-complementary sequences or hybridizes to a third nucleic acid strand, and which specific nucleic acid component directs synthesis of a nucleic acid product.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of nucleic acid delivery in organisms, and to illustrate the state of the art of gene

delivery, including antisense and other inhibitory oligonucleotides to target cells, tissues or organs.

Crooke teaches that the in vivo (whole organism) application of molecules is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target molecules. See, *e.g.*, Crooke, Progress in Antisense Technology, Ann. Rev. Medicine, Vol. 55, pages 61-95, at page 72:

> Given the variability in cellular uptake of oligonucleotides, the variability in potency as a function of binding site in an RNA target, and the potential nonantisense activities of oligonucleotides, careful evaluation of dose-response curves and clear demonstration of the antisense mechanism are required before drawing conclusions from in vitro experiments…

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using nucleic acid based approaches. Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy:

> A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate…cellular uptake following systemic administration appears to require more sophisticated formulations… the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field.

A. Peracchi et al, Rev. Med. Virol., 14: 47-64, 2004, at 51).

Peracchi teaches that the unpredictability of siRNA accurately reflects the art of gene therapy at the time of the instant invention:

> Nevertheless, it seems way too early to assume that the development of siRNAs will supersede the therapeutic use of catalytic nucleic acids... it must be appreciated that the technology based on siRNAs is new, and many important details of the mechanisms contributing to the effectiveness of siRNA in cells remain unclear… In addition, the application of siRNAs appears subject to some of the problems that afflict other kinds of oligonucleotide-based therapeutic approaches, including the need for efficient delivery systems and the dependence of the observed effect on the specific mRNA region against which the siRNAs are designed.

(bridging paragraph, pages 57-58 and first full paragraph on p. 58) (citations omitted).

Agrawal et al (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80): also speak to the unpredictable nature of the nucleic acid based therapy field thus:

> It is therefore appropriate to study each … oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide… Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense.

Both Chirila et al and Agrawal point to the current limitations which exist in our understanding of the cellular uptake of nucleic acids in sufficient amounts to effect a phenotype or desired effect in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic nucleic acids to target cells).

See also the discussion by Opalinska et al of unpredictability of nucleic acid therapy, including the use of siRNA and antisense in vivo (Opalinska et al,

Nature Rev., 1: 503-514, at 503 and 511). "Although conceptually elegant, the prospect of using nucleic-acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain… The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field. …it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression in vivo is quite variable, and therefore wanting in terms of reliability." (citations omitted).

See also Jang et al (Expert Rev. Medical Devices, Vol. 1, No. 1, pages 127-138, 2004), describing the field of nucleic acid delivery devices, including medical implants, as being in the early stages of development, addressing some of the variables affecting in vivo success:

> …Prior to cellular internalization however, the vector may interact with the polymer scaffold and other components in the extracellular milieu. These interactions can influence vector release from the scaffold, stability, transport through the extracellular space, and ultimately internalization and trafficking. (left column and page 135).

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to kits and methods of administering nucleic acid compositions to any cell in an organism comprising introducing nucleic acid constructs comprising a first, second and third nucleic acid strand, which first nucleic acid strand is circular, is hybridized to the second nucleic acid

strand to from a double stranded portion, and which first nucleic acid strand is also hybridized to a third nucleic acid strand in forming a gapped circle, and which second nucleic acid strand is fully complementary and hybridizes with the first nucleic acid strand, and which second nucleic acid strand is double stranded and forms a template for synthesis of a nucleic acid product when present in a prokaryotic or eukaryotic cell, and which third nucleic acid strand also comprises a tail which is covalently attached to an antibody, and also hybridizes to a fourth nucleic acid strand, which is also covalently attached to an antibody. The claims are also drawn to compositions comprising any non-natural entity comprising a first domain which binds non-covalently to a specific nucleic acid component and comprises a linear nucleic acid strand that is complementary to a specific nucleic acid component, and further comprising a second domain which is an entity that binds non-covalently to a cell of interest, and which second domain is separated from the first domain by extension of a specific nucleic acid strand which comprises two separate double stranded regions, one which is bound to the non-natural entity and hybridizes with the first domain's nucleic acid strand, and wherein the second double stranded region forms either through self complementary sequence or hybridizes to a third nucleic acid strand, and which specific nucleic acid component directs synthesis of a nucleic acid product.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues, whereby a representative number of the nucleic acid structures representing this

diverse and expansive genus claimed are successfully delivered to the target cells or tissues in vitro or in vivo intact, and further whereby recombinant expression is provided from the intact constructs in vitro and in the intended target cells in a subject.

Since the specification fails to provide any particular guidance or concrete examples for the successful targeting or delivery of a representative number of species of the broad genus of compounds claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention using the broad array of constructs claimed.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of delivery of a representative number of species, or any concrete examples in vitro or in vivo. Applicants have not provided adequate written description for the compositions claimed, nor the successful use of any representative number of species of the broadly claimed genus whereby any concrete examples of intact delivery and recombinant expression are provided.

The disclosure teaches schematics of nucleic acid constructs comprising multiple nucleic acid components (3 and 4 segment components) and domains for target cell binding (see figures 4, 6, 15-8) and for recombinant expression in a target cell. But no reduction to practice has been provided for the instant schematics, whereby the proposed structures are successfully targeted to and transfected into target cells, remain intact as schematically depicted, and

produce the recombinant nucleic acids or protein expression products in a predictable manner.

In vivo results require undue experimentation, and cannot be generalized from a test tube (or cell culture) to an organism. One skilled in the art would not accept on its face the examples of schematics given in the specification as being correlative or representative of the successful in vivo delivery, or of concrete examples of a representative number of species, in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the targeting ability of these multi-component nucleic acid structures in any organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery, and specifically regarding the instant array of compositions claimed.

For these reasons, it would require undue experimentation beyond that provided in the instant specification to make and use the array of constructs as instantly claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or

applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** The examiner's office hours are generally Monday-Friday, 10:30am - 7pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Low, can be reached on (571) 272-0951. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
8-6-10

/Jane Zara/

Primary Examiner, Art Unit 1635